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IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT
APPEALS AND INTERFERENCES

Serial No. : 10/524,996

Applicants : Hiroyuki ASADA et al.

Filed : February 18, 2005

For : STABLE OPHTHALMIC SOLUTION COMPRISING LATANOPROST AS...

Art Unit : 1612

Examiner : Walter E. WEBB

Docket No. : 05105/HG

Confirm. No. : 3212

Customer No. : 01933

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Richard S. Barth

Attorney: Richard S. Barth

Dated: September 30, 2009

In the event that this Paper is late filed, and the necessary petition for extension of time is not filed concurrently herewith, please consider this as a Petition for the requisite extension of time, and to the extent not tendered by Form PTO-2038 attached hereto, authorization to charge the extension fee, or any other fee required in connection with this Paper, to Account No. 06-1378.

APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

MAIL STOP APPEAL BRIEF - PATENTS

S I R :

Appellants hereby appeal the Final Rejection of claims 6, 8, 10, 12, 14 and 16 of the above-identified application, as set forth in the Office Action (Final Rejection) mailed February 20, 2009.

A Notice of Appeal was filed in the USPTO with the appropriate fee on August 18, 2009.

Accordingly, this Appeal Brief is being timely filed by the due date of October 18, 2009.

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A Form PTO-2038 authorizing a charge of $540.00 is submitted herewith in payment of the fee set forth in 37 CFR 41.20(b)(2).

In addition, authorization is hereby given to charge any additional fees which may be determined to be required, or credit any overpayment, to Deposit Account 06-1378.

(i) REAL PARTY IN INTEREST

The real party in interest is SANTEN PHARMACEUTICAL CO., LTD., a corporation of Japan, having a place of business at 9-19, Shimoshinjo 3-chome, Higashiyodogawa-ku, Osaka-shi, Osaka 533-8651 Japan.

(ii) RELATED APPEALS AND INTERFERENCES

There are no related appeals and interferences.

(iii) STATUS OF CLAIMS

This is an appeal from the Final Rejection dated February 20, 2009 rejecting claims 6, 8, 10, 12, 14 and 16.

Claims 1 to 5, 7, 9, 11, 3, 15 and 17 were canceled.

The appealed claims (claims 6, 8, 10, 12, 14 and 16) are set forth in the attached Appendix.

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(iv) STATUS OF AMENDMENTS

An AMENDMENT UNDER 37 CFR 1.116 was filed on July 20, 2009 in response to the Office Action (Final Rejection) mailed February 20, 2009. In the ADVISORY ACTION mailed July 31, 2009, it was indicated that, for purposes of appeal, the aforesaid AMENDMENT UNDER 37 CFR 1.116 would be entered. Thus, the appealed claims are claims 6, 8, 10, 12, 14 and 16, as set forth in the AMENDMENT UNDER 37 CFR 1.116 filed July 20, 2009.

The application filed on February 18, 2005 contained claims 1 to 4. In an AMENDMENT UNDER 37 CFR 1.116 filed January 18, 2008, claims 1, 3 and 4 were amended and claims 2 was canceled. In an AMENDMENT FILED CONCOMITANTLY WITH RCE filed April 17, 2008, claim 1 was amended, claims 3 and 4 were canceled and claims 5 to 17 were added. In the AMENDMENT UNDER 37 CFR 1.111 filed October 30, 2008, claims 1 and 5 were canceled and claim 6 was amended. In said AMENDMENT UNDER 37 CFR 1.116 filed July 20, 2009, claim 6 was amended and claims 7, 9, 11, 13, 15 and 17 were canceled.

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(v) SUMMARY OF CLAIMED SUBJECT MATTER

The present claims are directed to an aqueous ophthalmic solution containing latanoprost which is stabilized to be stored at room temperature (see the first paragraph on page 1 of the specification).

Latanoprost is a prostaglandin that is used to treat glaucoma. The chemical name of latanoprost is isopropyl (Z)-7(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptanoate. Latanoprost is a selective FP receptor agonist and lowers intraocular pressure by promoting the outflow of an aqueous humor. The administration route of latanoprost is instillation.

The commercially available ophthalmic solution of latanoprost lacks stability. It is thus necessary to store the commercially available ophthalmic solution of latanoprost in a cold environment (2° to 8°C) and to shield it from light (see the last two paragraphs on page 1 of the specification).

It has been desired to develop a latanoprost ophthalmic solution which can be stored at room temperature and has an excellent stability.

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Appellants' presently claimed invention solves the above-discussed problems and desires.

Appellants' independent claim 6 is directed to an aqueous ophthalmic solution comprising 0.005% (W/V) latanoprost as an active ingredient, wherein the latanoprost is stabilized to be stored at room temperature by adding ε-aminocaproic acid to the solution (see the following portions of the specification: the fourth paragraph on page 2; the paragraph bridging pages 2 and 3 and the first full paragraph on page 3).

Appellants' independent claim 12 concerns an aqueous ophthalmic solution comprising 0.005% (W/V) latanoprost as an active ingredient, wherein the latanoprost is stabilized to be stored at room temperature by adjusting the pH of the solution to 5.0 to 6.25 and adding ε-aminocaproic acid to the solution (see the following portions of the specification: the paragraph bridging pages 2 and 3 and the first full paragraph on page 3).

(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The ground of rejection presented for review is whether claims 6, 8, 10, 12, 14 and 16 are rendered obvious by USP

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6,011,062 to Schneider et al. in view of USP 5,556,848 to Kimura et al.

(vii) ARGUMENT

Claims 6, 8 and 10

Admissions in the Office Action

It was admitted in the Office Action of June 2, 2008 that Schneider et al. differ from the instant claims insofar as Schneider et al. do not teach adding ε-aminocaproic acid to an ophthalmic solution.

It was further admitted in the Office Action of June 2, 2008 that Kimura et al. do not teach the use of latanoprost.

Schneider et al.

Schneider et al. teach storage-stable prostaglandin compositions and disclose that the use of polyethoxylated castor oils in the compositions enhances the chemical stability of the prostaglandins in the compositions (column 1, lines 52 to 56 of Schneider et al.). Further, Figs. 1 and 2 of Schneider et al. show that the addition of polyethoxylated castor oils (Cremophor® EL and Alkamuls® EL-620) increases the chemical stability of

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prostaglandin (Compound No. 2) as compared with the case where a surfactant (Polysorbate 80) is added.

However, the polyethoxylated castor oil used in Schneider et al. is a polymer classified as PEG-5 to PEG-200 hydrogenated castor oils, whereas ε-aminocaproic acid used in the appellants' claims is a low-molecular compound represented by the following formula: $H_2NCH_2CH_2CH_2CH_2COOH$. Polyethoxylated castor oil used in Schneider et al. and ε-aminocaproic acid recited in appellants' claims completely differ from each other in their chemical structure and their chemical properties. This difference was acknowledged at the bottom of page 2 of the February 20, 2009 Office Action.

Kimura et al.

Kimura et al. (USP 5,556,848) disclose an ophthalmic suspension comprising difluprednate. Difluprednate is an anti-inflammatory and anti-allergic steroid.

Kimura et al. also disclose that a water soluble polymer (such as hydroxypropylmethylcellulose or polyvinyl alcohol) is added to the water-insoluble difluprednate for enhancing its dispersion in an ophthalmic suspension (column 2,

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lines 27 to 37 of Kimura et al.). Kimura et al. further disclose that nonionic surfactants, such as polyoxyethylene hydrogenated castor oils can be added in their suspension for enhancing the dispersion stability (column 3, lines 34 to 49 of Kimura et al.).

Moreover, Kimura et al. disclose in column 3, lines 19 to 33 that acetates and ε-aminocaproic acid are useful as buffers to suppress the formulation of agglomerates, prevent the lowering of pH, and provide a suspension superior in redispersibility and stability.

As discussed above, Kimura et al. teach enhancing the dispersion stability in an ophthalmic suspension containing water-insoluble difluprednate (physical stabilization). In contrast thereto, appellants' claims concern enhancing the chemical stability of latanoprost dissolved in water (chemical stabilization). Stated differently, since the problem sought to be solved in Kimura et al. is to stabilize the dispersion of a suspended ophthalmic solution, whereas the appellants' claims seek to chemically stabilize an active ingredient (latanoprost) in a water-soluble ophthalmic solution, Kimura et al. and appellants' claims substantially differ from each other in what is stabilized.

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Further, since the active ingredient of Kimura et al. is difluprednate, whereas the active ingredient of appellants' claims is latanoprost, Kimura et al. and appellants' claims completely differ from each other also in the chemical structure and the chemical properties of the respective active ingredient. This difference is acknowledged at the bottom of page 2 of the February 20, 2009 Office Action.

Moreover, although Kimura et al. disclose that ε-aminocaproic acid enhances the dispersion stability of their suspended ophthalmic solution (which does not include latanoprost), there is no teaching or suggestion in Kimura et al. of the chemical stability of latanoprost in a water-soluble ophthalmic solution.

Combination of Schneider et al. and Kimura et al.

For the following reasons, it is respectfully submitted that a person of ordinary skill in the art would not consider to combine the references to attempt to arrive at appellants' claims. Moreover, even assuming *arguendo* that the references are combinable, it is respectfully submitted that the combination

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would not lead to a person of ordinary skill in the art to appellants' claims.

It is respectfully submitted that there is no reason for substituting the active ingredient in Schneider et al. (a prostaglandin) for the active ingredient in Kimura et al. (difluprednate), since these two active ingredients are totally different (as acknowledged in the February 20, 2009 Office Action).

Schneider et al. and Kimura et al. both employ a polymer. Kimura et al. disclose ε-aminocaproic acid only as an additional component, namely, a buffer. It follows that a person of ordinary skill in the art would not consider to employ ε-aminocaproic acid as a substitute for the polyethoxylated castor oils employed by Schneider et al.

Unexpected Results

Table 3 on page 16 of the specification (which is reproduced hereinbelow) shows that after storage at 50°C for 8 weeks, the residual ratio of the latanoprost in an ophthalmic solution is 93.1% when ε-aminocaproic acid is added to the solution. Moreover, Table 3 shows that after storage at 80°C for 4 weeks,

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the residual ratio of latanoprost is 51.8% when ε-aminocaproic acid is added, whereas the residual ratio of latanoprost is 6.3 to 28.9% when ε-aminocaproic acid is not added. Thus, appellants' Table 3 clearly shows that the stability of latanoprost in an aqueous ophthalmic solution is significantly improved when ε-aminocaproic acid, out of numerous additives, is added. This increased stability afforded by the presently claimed invention was acknowledged at the bottom of page 3 of the February 20, 2009 Office Action.

Appellants have informed the undersigned that in the field of ophthalmic solutions, the storage-stability of a drug at room temperature over a long period is generally presumed from an accelerated test conducted at a high temperature.

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	Additives	Storage at 50°C for eight weeks	Storage at 80°C for four weeks
Formulation 1	Crystalline sodium dihydrogenphosphate	88.7%	24.0%
Formulation 2	PEG 400	88.8%	25.9%
Formulation 3	Propylene glycol	88.1%	26.1%
Formulation 4	Trehalose	83.7%	26.4%
Formulation 5	Isopropanol	88.9%	28.9%
Formulation 6	α-Cyclodextrin	86.6%	22.1%
Formulation 7	Citric acid	87.1%	6.3%
Formulation 8 according to the presently claimed invention	ε-Aminocaproic acid	93.1%	51.8%

Claims 12, 14 and 16

Appellants' claims 12, 14 and 16 relate to a further enhancement of the chemical stability of latanoprost by adding ε-aminocaproic acid within a specified pH range of 5.0 to 6.25.

For the reasons discussed hereinabove with respect to appellants' claim 10, it is respectfully submitted that appellants' claim 12 patentably distinguishes over the references, either singly or combined.

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Unexpected Results

Unexpected results for employing a pH range of 5.0 to 6.25 (as recited in appellants' claim 12) is shown in appellants' Table 1 (on page 10 of the specification), which is reproduced hereinbelow.

Table 1 shows that the stability of latanoprost (residual ratio %) after storage for 28 days at 60°C and 70°C is substantially better at a pH of 5.0 to 6.25, compared to at a pH of each of 4.0, 6.7 and 8.0.

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Table 1

Stability of latanoprost (Residual ratio (%) after storage for 28 days)

	according to applicants' present claims						
	pH 4.0	pH 5.0	pH 5.5	pH 6.0	pH 6.25	pH 6.5	pH 6.7	pH 8.0
60 °C	87.4	98.9	98.0	98.9	95.0	92.4	93.4	30.0*
70 °C	76.7	94.9	94.6	93.1	92.0	82.7	78.1	14.1**

*Value on 21st day, ** value on 12th day

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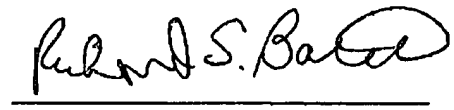
CONCLUSION

In view of the foregoing, it is respectfully submitted that appellants' claims 6, 8, 10, 12, 14 and 16 patentably distinguish over Schneider et al., alone or combined with Kimura et al.

Accordingly, it is respectfully requested that this Honorable Board reverse the rejection of appealed claims 6, 8, 10, 12, 14 and 16.

Respectfully submitted,



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Encs.: (1) Appendix of Appealed Claims
(2) Form PTO-2038 for $540

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(viii) INDEX OF APPEALED CLAIMS

6. An aqueous ophthalmic solution comprising 0.005% (W/V) latanoprost as an active ingredient, wherein the latanoprost is stabilized to be stored at room temperature by adding ε-aminocaproic acid to the solution.

8. The ophthalmic solution as claimed in claim 6, wherein the ε-aminocaproic acid is in a concentration of 0.1 to 2% (W/V).

10. The ophthalmic solution as claimed in claim 6, wherein the ε-aminocaproic acid is in a concentration of 1% (W/V).

12. An aqueous ophthalmic solution comprising 0.005% (W/V) latanoprost as an active ingredient, wherein the latanoprost is stabilized to be stored at room temperature by adjusting the pH of the solution to 5.0 to 6.25 and adding ε-aminocaproic acid to the solution.

14. The ophthalmic solution as claimed in claim 12, wherein the ε-aminocaproic acid is in a concentration of 0.1 to 2% (W/V).

16. The ophthalmic solution as claimed in claim 12, wherein the ε-aminocaproic acid is in a concentration of 1% (W/V).

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(ix) EVIDENCE APPENDIX

Not applicable

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(x) RELATED PROCEEDING APPENDIX

Not applicable

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